## REMARKS

Reconsideration of the rejections set forth in the Office Action dated February 8, 2006 is respectfully requested. A Petition for a three-month extension of time is enclosed, along with supporting Declarations, an IDS and copies of selected references therein, and a Terminal Disclaimer.

I. Amendments to the claims

Independent claim 1 is amended to recite a method of improving in a subject the pharmacokinetics of a drug that is metabolized by a drug-metabolizing cytochrome p450 enzyme, comprising co-administering with said drug, a morpholino antisense oligomer effective to reduce synthesis of the p450 enzyme by hybridizing to a target RNA molecule which encodes said enzyme, where the antisense oligomer (i) has a backbone containing phosphorodiamidate-linkages (basis on page 7, lines 19-21), (ii) a length of at least 15 nucleotides (basis on page 3, line 25), (iii) hybridizes to a target RNA that includes either the AUG translation start site, or, where the target RNA molecule is a pre-mRNA, a region of the pre-mRNA which includes an intron-exon boundary or an exon-intron boundary (basis on page 3, lines 21-24) , and (iv) forms with the target RNA molecule, a heteroduplex having a Tm greater than 37°C (basis on page 6, lines 6-8).

II. Rejections under 35 U.S.C. §112, First Paragraph

Claims 1-9, 13-15, and 25-30 were rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventors, at the time the application was filed, had possession of the claimed invention.

The Examiner contends that, "the claims read on the metabolism of any drug comprising administering antisense oligonucleotides targeting the broad genus of cytochrome p450 enzymes ... and all other allelic and polymorphic variants of cytochrome p450 enzymes," p. 2, Office action mailed February 8, 2006.

This rejection, to the extent it is applied to currently pending claims 1-9, 13-15, and 25-30, is respectfully traversed in view of the following arguments.

A. Legal standard for the written description requirement of 35 U.S.C. §112, first paragraph

The written description requirement of 35 U.S.C. §112, first paragraph, as it applies to a method of treatment claim, is discussed at length by the CAFC in *University of Rochester v. G.D. Searle & Co.*, 358 F.3d 916, 69 USPQ2d 1886 (Fed. Cir. 2004), a copy of which is enclosed.

In *Rochester,* the University's U.S. Patent No. 6,048,850 ("the '850 patent"), with claims directed to a method of selectively inhibiting PGHS-2 activity in a human host, comprising administering a non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product to a human host in need of such treatment, had been found invalid by the district court for failing to meet the written description requirement of 35 U.S.C. §112, first paragraph. The basis for this finding by the district court was that patent in suit "neither discloses any such compound nor provides any suggestion as to how such compound could be made or otherwise obtained other than by trial-and-error research." Indeed, the court found no evidence in the '850 patent that the inventors themselves knew of any such compound at the time their patent application was filed.

In affirming the district court's finding, the CAFC noted (p. 1895) that "[i]t is undisputed that the '850 patent does not disclose any compounds that can be used in its claimed method. The claimed methods thus cannot be practiced based on the patent's specification, even considering the knowledge of one skilled in the art. No compounds that will perform the claimed method are disclosed nor has any evidence been shown that such a compound was known...Rochester did not present any evidence that the ordinarily skilled artisan would be able to identify any compound based on its vague functional description as a 'non-steroidal compound that selectively inhibits activity of the PGHS-2 gene product.'"

The Rochester court cited *In re Edwards*, 568 F.2d 1349 [196 USPQ 465] (CCPA 1978), and *In re Herschler*, 591 F.2d 693 [200 USPQ 711] (CCPA 1979), in support of its decision. In *Herschler*, the court found adequate written description support for broad claims to processes for topically administering a physiologically active steroidal agent to a human or animal by concurrently administering the steroidal agent and dimethyl sulfoxide ("DMSO"), even though the specification disclosed only one example of a "physiologically active steroidal agent." Critically, however, there was no question

in that case that, unlike "non-steroidal compound[s] that selectively inhibit[ ] activity of the PGHS-2 gene product," numerous physiologically active steroidal agents were known to those of ordinary skill in the art. As the *Herschler* court noted, "[w]ere this application drawn to novel 'steroidal agents,' a different question would be posed." 591 F.2d at 701. The novelty in that invention was the DMSO solvent, not the steroids.

It is clear from *Rochester*, and particularly from the CAFC's treatment of the result in *Herschler*, that the written description requirement, as it applies to a method of treatment claim, does not require that every possible compound that could be encompassed by the claim must be disclosed in the patent specification (in contradistinction to composition claims, where the scope of the claim can be known typically only if the structures covered by the claim are disclosed). On the contrary, *Rochester* seems to suggest that a single compound, that is, any compound that would allow one to practice the claimed invention successfully, would be sufficient to meet the written description requirement.

The applicant is unaware of any case law or PTO guideline that indicates that a method of treatment claim must disclose every possible or even a plurality of different treatment compounds in order to meet the written description requirement, nor has the Examiner suggested any such case law.

As currently amended, the claimed method encompasses the use of phosphorodiamidate morpholino oligonucleotides (PMOs) whose sequences are directed against target RNA encoding a cytochrome P450 enzyme, and specifically, against the AUG translation start site or, where the target is a pre-mRNA, against a splice site region of the molecule, for improving the pharmacokinetics of a drug that is metabolized by the P450 enzyme. The specification discloses twelve different sequences (SEQ ID NOs: 16, 18-25, 35, and 46-47) directed against four different P450 RNA targets (CYP2B1, CYP2E1, CYP3A2 and CYP3A4) that were shown in the specification, e.g., Examples 1-5, to be effective in inhibiting P450 activity, and thus in inhibiting metabolism of drugs that are substrates for the P450 enzymes. The Examiner's attention is also directed to the results described in the enclosed Iversen Declaration, dated February 27, 2002, wherein Taxol activity was enhanced by co-administration of an anti-CYP3A4 morpholino oligomer, in accordance with the claims.

Accordingly, the specification discloses several different PMO targeting sequences, directed to several different enzyme targets that were effective in inhibiting expression of the target enzymes, and thus effective in inhibiting metabolism of coadministered drugs metabolized by those enzymes. In view of the standards for written description established in the case law for method-of-treatment claims, Applicant respectfully submits that the claimed invention meets the written description requirement of 35 U.S.C. §112, first paragraph. Withdrawal of the rejection is respectfully requested.

B. Legal standard and application for the enablement requirement of 35 U.S.C. §112, first paragraph

Claims 1-9, 13-15, and 25-30 were rejected under 35 U.S.C. §112, first paragraph, as allegedly containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to make and use the invention without undue experimentation.

The Examiner advances two primary arguments: (1) unpredictability in the antisense art and (2) a lack of evidence that cytochrome p450 enzymes can metabolize every known conceivable drug. These arguments are addressed in turn.

1. Rebuttal to alleged unpredictability in the antisense art – PMOs do not show significant variation and have widely reproducible effects

With respect to an alleged unpredictability regarding the behavior of antisense compounds *in vivo*, the Examiner relies on oft-cited articles (Crooke, Branch, and Stein) on antisense technology which describe unpredictable effects, difficulty in cell uptake, nonspecific effects, etc. However, these articles discuss almost exclusively phosphorothioate oligonucleotides, or, in some cases, other charged-backbone oligonucleotides, such as phosphodiesters (native DNA). The Stein article is concerned with cleavage caused by RNAse competent oligomers, which include phosphorothioates and phosphodiesters (page 232, column 1, first paragraph), but not morpholino oligomers.

Phosphorothioate oligonucleotides (PS-ONs) have shown significant variation in cellular uptake, inhibition of protein synthesis, and RNA degradation. In contrast, the

phosphorodiamidate morpholino oligomers (PMOs) of the claimed invention do not exhibit these deficiencies. At the time of filing of the application, morpholino oligomers had been shown to provide significantly improved selectivity in inhibiting translation of targeted sequences in comparison to the widely used phosphorothioate oligonucleotides. The morpholino oligomers were also shown to inhibit translation at much lower concentrations than the corresponding phosphorothioates, and with little or no evidence of the substantial non-antisense activity exhibited by the phosphorothioates. *See*, for example, Summerton et al., Antisense & Nucleic Acid Drug Dev 7 (2) p.63-70, Apr 1997, copy enclosed. The vast majority of the morpholino oligomers encompassed by the claims have been shown to be effective in the Examples in the specification (including *in vivo* experiments 3 and 5).

The use of such oligomers in antisense applications has been shown to overcome many of the drawbacks which are associated with charged antisense oligonucleotide analogs, such as the widely used PS-ONs. Nonspecific effects observed with charged, RNAse-competent oligomers, such as the phosphorothioates, are generally attributed to nonspecific binding, both to nontargeted nucleic acids and to cellular proteins, and nonspecific RNAse activation (which cleaves nontarget RNA, as shown in Fig. 1 of Branch). These effects are greatly reduced by the use of morpholino oligomers, in large part due to their minimal charge, or lack of charge, and mechanism of action, which is based on steric blocking rather than RNAse-mediated cleavage of the target. Thus, the morpholino oligomers do not cause "irrelevant cleavage" of the target RNA as noted by the Examiner at page 7 of the Office action mailed February 8, 2006 in citing Stein, as they are RNAse inactive compounds. Accordingly, while the PS-ONs of the prior art have shown variation and unpredicability, the PMOs of the claimed invention do not show these deficiencies and are widely reproducible.

For example, in Zhang et al. (Antiviral Research, 2006 *in press*; copy enclosed), antisense peptide-conjugated PMO (P-PMO) specifically suppressed protein expression of Kaposi's scarcoma-associated herpesvirus (KSHV) by 98% in comparison to a mock treatment control. The P-PMO showed no detectable cytotoxicity under the conditions used. In Zhang et al. (Veterinary Microbiology, 2006 *in press*, copy enclosed), in a cell culture assay, PMOs reduced viral titer of porcine reproductive and respiratory

syndrome virus (PRRSV) by 214-fold relative to mock treatment. The percentage of viable cells was nearly identical between PMO-treated and mock-treated cells, demonstrating that the P-PMOs were not cytotoxic under these conditions. Further, a recently completed Phase II clinical study, described in the enclosed Declaration executed by co-inventor Dr. Dwight Weller, showed efficacy in a patient population having existing recurrent restenosis following PTCA, and selected based on criteria targeting patients with a high probability of restenosis. As described in the Weller Declaration, patients receiving an anti-*c-myc* morpholino oligomer showed significantly less reocclusion than patients receiving a subtherapeutic dose or receiving no oligomer. No drug related serious adverse effects were observed. Thus, these recent studies are good examples of the successful and reproducible use of PMOs. They show increased target specificity and cellular viability over previous antisense approaches, including the PS-ONs.

In contrast, Opalinska et al. (Science's STKE, 2003; copy enclosed) discuss the use of PS-ONs in various settings including clinical trials. The review concedes that "[a]s in other studies with phosphorothioate oligonucleotides ... no complete or partial results were achieved," Id. at 3.

Also enclosed is a second Declaration under 37 CFR §1.132, signed by the inventor, Patrick L. Iversen, and copies of several references discussed in the Iversen Declaration. These materials describe how morpholino oligomers having substantially uncharged, phosphorus-based linkages have shown sequence-specific antisense activity *in vivo* in a variety of animal models and targets. As demonstrated by the Declarations and enclosed references, morpholino oligomers having substantially uncharged, phosphorus-based linkages have shown sequence-specific antisense activity *in vivo* in a variety of animal models and targets, thus establishing a pattern of *in vivo* efficacy for these oligomers.

2. <u>The claims do not broadly encompass the inhibition of any drug and the quantity of experimentation required to practice the invention is not undue</u>

With respect to the assertion that the instant claims broadly encompass the inhibition of the metabolism of <u>any drug</u> by means of co-administration of a morpholino

antisense oligomer targeting cytochrome p450 enzymes, it is noted that claim 1 is amended to recite a method of improving in a subject the pharmacokinetics of a drug that is metabolized by a drug-metabolizing cytochrome p450 enzyme. Thus, the claim requires that the drug be metabolized by a drug-metabolizing cytochrome p450 enzyme.

Further, the amount of experimentation required to practice the invention cannot be considered not undue, as the Examiner alleges at p. 8 of the Office action. The specification describes *in vivo* efficacy of antisense morpholino oligomers used in accordance with the claims, for inhibiting metabolism of a drug by a P450 enzyme. Cell uptake and nuclease resistance of uncharged morpholino oligomers have been demonstrated by experiments in which the oligomer is administered to a mammal and can be detected several hours later in body fluids, in the form of a duplex with the target mRNA (PCT Pubn. Nos. WO 2000/45167 and WO 2002/48405; see also the present specification at page 10, lines 19-27.). This assay shows that the oligomer enters cells and binds with target mRNA, and that the resulting duplex is resistant to nuclease digestion. The assay can also be used as a simple test for *in vivo* hybridization of a given oligomer to its target sequence. Thus, it would be well within the ability of one skilled in the art to test binding of oligomers to target sequences, both *in vitro* (e.g., by measurement of Tm) and *in vivo* (by detection of heteroduplexes as described at page 10, lines 19-27).

The Specification also provides detailed guidelines regarding various modes of delivery in a whole organism. For example, at p. 22, line 26 through p. 23, line 7, various routes of administration of antisense oligomers are disclosed:

> The routes of administration of antisense oligomers include, but are not limited to, various systemic routes, including oral and parenteral routes, e.g., intravenous, subcutaneous, intraperitoneal, intramuscular, and intraarterial injection, as well as inhalation and transdermal delivery. In some cases, targeted delivery by direct administration to a particular tissue or site is preferred. It is appreciated that any methods which are effective to deliver the drug to a target site or to introduce the drug into the bloodstream are also contemplated.
>
> Examples of standard pharmaceutically accepted carriers include saline, phosphate buffered saline (PBS), water, aqueous ethanol, emulsions such as oil/water emulsions, triglyceride emulsions, wetting agents, tablets and capsules. It will be understood that the choice of

suitable physiologically acceptable carrier will vary dependent upon the chosen mode of administration.

Specific dosages for different routes of administration are also disclosed at p. 23, lines 21-28:

> In practicing the method of the invention, the antisense oligomer is co-administered with the drug at a desired dose and dosing schedule. Preferably, the oligonucleotide is first administered several hours to several days before first administering the drug, to allow reduction of the target enzyme level. Preferred doses for oral administration are between about 1-2 mg oligomer/kg patient body weight, assuming an oligonucleotide MW of about 7000. A typical therapeutic dose for a patient weigh[ing] 70 kg would thus be about 70 mg administered once a day, although higher doses may be administered if needed. For IV administration, the preferred doses are about 1/3 the oral dose.
>
> It is noted that co-administration of an antisense oligomer with a drug may be concurrent with, following, or preferably preceding administration of the drug, as long as the antisense oligomer is effective to modulate metabolism and enhance the efficacy of the drug.

In accordance with the claimed method, one co-administers with the drug a morpholino antisense oligomer effective to reduce synthesis of the drug-metabolizing cytochrome p450 enzyme, by hybridizing to a target RNA molecule which encodes the enzyme. The ability of the claimed morpholino antisense oligomers to bind to target RNA is described in the Specification at page 11, lines 25-34. There, reference is made to co-owned PCT Publication WO 00/45167 (copy enclosed), which, as stated above, presents in Example 2 *in vivo* evidence of the ability of a phosphoramidate morpholino oligonucleotide antisense to rat cytochrome P-4503A2 to form a heteroduplex with target RNA. Thus, no undue experimentation is needed to practice the claimed method.

In view of the foregoing, the applicant submits that the amended claims and specification comply with the requirements of 35 U.S.C. §112, first paragraph.

III. Obviousness-Type Double Patenting Rejection

Claims 1-9, 13-15, and 25-30 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-15 of U.S. Patent No. 6,673,778 B1.

A Terminal Disclaimer prepared in accordance with 37 C.F.R. §1.321(b) and (c) is enclosed. The signed Terminal Disclaimer obviates this obviousness-type double patenting rejection and withdrawal of the rejection is respectfully requested.

## IV. CONCLUSION

In view of the foregoing, Applicant submits the claims pending in the application are in condition for allowance. A Notice of Allowance is therefore respectfully requested.

If in the opinion of the Examiner, a telephone conference would expedite the prosecution of the subject application, the Examiner is encouraged to call the undersigned at (650) 838-4341.

The Commissioner is hereby authorized and requested to charge any deficiency in fees herein, or credit any overpayment, to Deposit Account No. **50-2207**.

Respectfully submitted,
Perkins Coie LLP

Date: August 8, 2006

/Gina C. Freschi/
Gina C. Freschi
Registration No. 52,062

**Correspondence Address:**
Customer No. 22918
(650) 838-4300